Cutaneous reaction to 
psycotropes

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No conflict of interest to disclose
Objectives

- Psychotropes and exacerbation/trigger of common skin conditions
- Common skin drug reaction
- Uncommon skin drug reactions
- Familiarise with methods of diagnosis
Psychotropes

- **Trigger** of underlying skin condition
- **Exacerbation** of underlying skin condition
- Adverse cutaneous reaction (allergic vs other)
Psychiatric disorder and the skin

• Skin conditions are often associated or precipitated by stress/stress disorders
  – Acne
  – Alopecia areata
  – Atopic dermatitis
  – Seborrheic dermatitis
  – Psoriasis
  – Rosacea
  – Pruritis
  – Psychogenic purpura
  – Urticaria
Pruritus

- Associated with psychiatric disease
  - Face and scalp high correlation with psychiatric diagnosis
- Associated with common skin condition (atopic)
- Can be manifestation of drug reaction
- Common in elderly
- Can be symptom of underlying internal disease
Psychotropes and trigger/exacerbation of common skin conditions

- Acne
- Alopecia
- Psoriasis
- Pruritus
- Photosensitive reaction
- hyperhidrosis
- Drug eruption
  - Eczema-like
  - Urticaria
  - Others…
- Acne
  - Lithium
  - Anticonvulsants
  - SSRIs

- Psoriasis
  - Lithium
  - Anticonvulsants
  - SSRIs
Comparison

- Skin conditions are often associated or precipitated by stress/stress disorders
  - Acne
  - Alopecia areata
  - Atopic dermatitis
  - Seborrheic dermatitis
  - Psoriasis
  - Rosacea
  - Pruritus
  - Psychogenic purpura
  - urticaria

- Psychotropes and trigger/exacerbation of common skin conditions
  - Acne
  - Alopecia
  - Psoriasis
  - Pruritus
  - Photosensitive reaction
  - Hyperhidrosis
  - Drug eruption
    - urticaria
Mood stabilisers-most common

- Anticonvulsants
  - Alopecia
  - Pruritus
  - Acneform eruption
  - Psoriasis
  - Hyperhidrosis
  - Drug eruption (out of all psychotropes, the mood stabilisers are ones with most risk for severe ACDRs)
    - Vasculitis (carbamazepine, gabapentin, sodium valproate)
    - EM/SJS, exfoliative, DRESS

- Lithium
  - Acne
  - Psoriasis
  - Alopecia
  - Folliculits
  - Drug reaction
Antidepressants (2nd most common)

- Photosensitivity
- Alopecia (ex. imipramine, desipramine, maprotiline, fluoxetide)
- Hyperhidrosis
- Particularities with the selective serotonin reuptake inhibitors
- Drug eruption
  - Maculopapular
  - Urticaria
  - Very rare SJS/TEN-fluoxetine, venlafaxine
  - Vasculitis/LCV- amitriptyline, maprotiline, trazodone, paroxetine, fluoxetine
Antidepressant - SSRI

- Spontaneous bruising/petechiae (blockade of serotonin reuptake in platelets causing plt dysfunction)
- Acneiform eruption (face, chest, back)
- Psoriasis flare
- Reversible Alopecia
- Hypertrichosis/hirsuitism
- Dyschromia (after many yrs of tx-hyperpigmentation skin, hair, nails)
- Photoallergic/phototoxic rxn
Antipsychotics (less common)

- Photosensitivity
  - Slate-gray discoloration in dun-exposed areas
- Skin Pigmentation changes
- Drug eruption
  - Exanthematous
  - Urticaria, angioedema
    - Risperidone, ziprasidone, droperidol, chlorpromazine
  - Pruritus
  - Vasculitis ex. olanazapine
Photosensitisers

• Photo-toxic
  • Common, dependant on UV dose, appears as a sunburn reaction, quick resolution

• Photo-allergic
  – Lower frequency, needs sensitisation from the allergen (requires UV for conversion), eczema/erythema multiforme, delay onset, longer duration (type IV mediated)
Photosensitisers

- **Phenothiazines**
  - Chlorpromazine (PA)
  - Thiordazine (lichenoid lesions with pigmentation)
  - Promethazine (PA)
  - chlorproethazine

- **Antidepressants**
  - Clomipramine
  - Imipramine
  - Sertraline
  - Desipramine
Cutaneous drug eruption

CADR Among most frequent of adverse effect

2-5% incidence among psych pts using psychotropes (sl higher then other med groups)
Immunologically Mediated Drug Reactions

- **IgE-dependent drug reactions (formerly type I, Gell–Coombs classification):**
  - urticaria, angioedema and anaphylaxis
- **Cytotoxic drug-induced reactions (antibody against a fixed antigen; formerly type II):**
  - petechiae secondary to drug-induced thrombocytopenia
- **Immune complex-dependent drug reactions (formerly type III):**
  - vasculitis, serum sickness and certain types of urticaria
- **Possible delayed-type, cell-mediated drug reactions (formerly type IV) versus undefined: (Types a,b,c,d)**
  - exanthematous, fixed and lichenoid drug eruptions, as well as Stevens–Johnson syndrome (SJS) and TEN.
Allergic cutaneous reaction (type I)

- Urticarial/angioedema
- Anaphylaxis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Delay</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urticaria</td>
<td>&lt;10 min</td>
<td>Penicillins, Cephalosporins, NSAIDs, Monoclonal antibodies, Contrast media</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>30 min</td>
<td>Penicillins, Cephalosporins, NSAIDs, Monoclonal antibodies, Contrast media</td>
</tr>
</tbody>
</table>
# Etiologies and Pathomechanisms of Urticarial Lesions

<table>
<thead>
<tr>
<th>Idiopathic</th>
<th>Immunologic</th>
<th>Non-immunologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune</td>
<td>• Autoimmune (autoantibodies against FceRI or IgE)</td>
<td>• Direct mast cell-releasing agents (e.g. opiates)</td>
</tr>
<tr>
<td></td>
<td>• IgE-dependent (allergic)</td>
<td>• Vasoactive stimuli (e.g. nettle stings)</td>
</tr>
<tr>
<td></td>
<td>• Immune complex (vasculitic)</td>
<td>• Aspirin, other non-steroidal anti-inflammatory drugs, dietary pseudoallergens</td>
</tr>
<tr>
<td></td>
<td>• Complement- and kinin-dependent (C1 esterase inhibitor deficiency)</td>
<td>• Angiotensin-converting enzyme inhibitors</td>
</tr>
</tbody>
</table>
Adverse cutaneous drug reaction
Allergic mediated (Type IV)

- Maculo-papular
- Eczema-like eruption
- Fixed drug
- AGEP
- SJS/TEN
- DRESS
<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Percentage that are drug-induced (%)</th>
<th>Time interval</th>
<th>Mortality (%)</th>
<th>Selected responsible drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exanthematous eruption</td>
<td>Child: 10–20 Adult: 50–70</td>
<td>4–14 days</td>
<td>0</td>
<td>Aminopenicillins Sulfonamides Cephalosporins Anticonvulsants Allopurinol</td>
</tr>
<tr>
<td>Urticaria Anaphylaxis</td>
<td>&lt;10 30</td>
<td>Minutes to hours Minutes to hours</td>
<td>0</td>
<td>Penicillins Cephalosporins NSAIDs Monoclonal antibodies Contrast media</td>
</tr>
<tr>
<td>Fixed drug eruption</td>
<td>100</td>
<td>First exposure: 1–2 weeks Re-exposure: &lt;48 hours, usually within 24 hours</td>
<td>0</td>
<td>TMP-SMX NSAIDs Tetracyclines Pseudoephedrine [*]</td>
</tr>
<tr>
<td>Acute generalized exanthematous pustulosis (AGEP)</td>
<td>70–90</td>
<td>&lt;4 days</td>
<td>1–2</td>
<td>β-Lactam antibiotics Macrolides Calcium channel blockers</td>
</tr>
<tr>
<td>Drug reaction with eosinophilia and systemic symptoms (DRESS) [*]</td>
<td>70–90</td>
<td>15–40 days</td>
<td>5–10</td>
<td>Anticonvulsants Sulfonamides Allopurinol Minocycline Lamotrigine (especially in combination with valproate)</td>
</tr>
<tr>
<td>Stevens–Johnson syndrome (SJS)</td>
<td>70–90</td>
<td>7–21 days</td>
<td>5</td>
<td>Sulfonamides Anticonvulsants</td>
</tr>
<tr>
<td>Toxic epidermal necrolysis (TEN)</td>
<td></td>
<td></td>
<td>30</td>
<td>NSAIDs Allopurinol</td>
</tr>
</tbody>
</table>
### Adverse cutaneous reaction (type III)

#### Vasculitis

<table>
<thead>
<tr>
<th>Disorder</th>
<th>First-line treatment</th>
<th>Evidence levels</th>
<th>Second-line treatment</th>
<th>Evidence levels</th>
<th>Third-line treatment</th>
<th>Evidence levels</th>
</tr>
</thead>
</table>
| Cutaneous small vessel vasculitis | Discontinue incriminated drugs  
Supportive care  
Treat underlying infections, neoplasms                                                |                 | Colchicine (0.6 mg bid-tid)          | 2               | AZA (2 mg/kg/day) MTX          | 3               |
Common skin drug reaction

- Maculo-papular
- Urticaria/angioedema
- Fixed drug eruption
- AGEP
Fixed Drug Eruption

- Single dusky erythematous plaque a few hours after oral TMP/SMX
- Residual grayish hyperpigmentation
AGEP

- Onset 1-2 days after drug intake
- T° & sudden eruption of multiple, 1-4 mm sterile pustules
- Starts on face and folds
- Becomes widespread in a few hours
- Marked neutrophilic leukocytosis
- Resolves in 1-2 weeks with desquamation
Uncommon skin drug reactions

- SJS/TEN
- Anaphylaxis
- Dress
- vasculitis
<table>
<thead>
<tr>
<th>Clinical entity</th>
<th>SJS</th>
<th>SJS–TEN</th>
<th>TEN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary lesions</strong></td>
<td>Dusky and/or dusky red lesions&lt;br&gt;Flat atypical targets</td>
<td>Dusky and/or dusky red lesions&lt;br&gt;Flat atypical targets</td>
<td>Poorly delineated erythematous plaques&lt;br&gt;Epidermal detachment–spontaneous or by friction&lt;br&gt;Dusky red lesions&lt;br&gt;Flat atypical targets</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>Isolated lesions&lt;br&gt;Confluence (+) on face and trunk</td>
<td>Isolated lesions&lt;br&gt;Confluence (++) on face and trunk</td>
<td>Isolated lesions (rare)&lt;br&gt;Confluence (+++) on face, trunk and elsewhere</td>
</tr>
<tr>
<td><strong>Mucosal involvement</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Systemic symptoms</strong></td>
<td>Usually</td>
<td>Always</td>
<td>Always</td>
</tr>
<tr>
<td><strong>Detachment (% BSA)</strong></td>
<td>&lt;10</td>
<td>10–30</td>
<td>&gt;30</td>
</tr>
</tbody>
</table>
• Preferentially extremities and face; target lesions favour the upper extremities
• Primary mucosal lesions vesiculobullous
• Rapidly develop painful erosions involving buccal mucosa, lips, ocular and genital mucosae
• Fever, lymphadenopathy, hepatitis and cytopenias
• Keratinocyte apoptosis is clearly a hallmark of the early stages of SJS and TEN
DRESS: danger signals

- Severe maculopapular, erythrodermic or bullous eruption
- Facial edema
- Fever and constitutional symptoms
- Adenopathies
- Hepatitis, at times fulminant (10% mortality)
- Interstitial pneumonitis, myocarditis, nephritis
- Eosinophilia
- Atypical lymphocytosis
Diagnostic approach

- Clinical and morphology
- Exam: Morphology consistent w drug eruption
- Differential Dx: Could it be something else?
- Chronology of drug exposure (timeline)
- Literature review: most & least likely culprits
- Tests (bloods, bx, patch & prick & ID tests, RAST)
- Dechallenge (Withdrawal of drugs)
- Rechallenge (Provocation test - potentially risky)
- Final etiological Dx: certain, probable, possible
# Drug Eruption Timeline

<table>
<thead>
<tr>
<th>Day:</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>14</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rx:</th>
<th>Amoxicillin 500 mg TID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrochlorothiazide 50 mg/d</td>
<td></td>
</tr>
<tr>
<td>Synthroid 150 μg/d</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Eruption</th>
<th>Clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Role of patch testing/skin test

- To better pinpoint the causative drug in face of multidrug use
- To allow the reintroduction some drugs
- To determine cross-reactions between drugs of the same class
- To select a substitute drug
- To distinguish between sensitization to active drug vs inert ingredients
Specifics of patch testing in drug eruptions

- Test 6 weeks to 6 months after eruption
- No immunosuppressant x 1 month
- Reading after 30 minutes, especially if eruption was urticarial
- Test over the area that was most affected:
  - Preferable in all cases
  - Essential in fixed drug eruption
When patch testing are negative

- **Prick Tests**
  - Use same aqueous solutions as for PT
  - When testing for urticaria, dilute as per ID tests
  - Read after 20 minutes and 24 hours

- **Intradermal Tests (ID tests)**
  - When prick tests are negative
  - Sterile sequential dilutions (10^{-4} to 100%)
  - Inject 0.04 ml - + if initial papule 2x in size
  - Read after 30 minutes, 24 et 96 hours
Sensitivity of skin tests

- Overall, patch tests are positive in 40 - 50% of cases.
- Has been useful with some psychotropes, ex. Paroxetine, Lamotrigine.
- Combining patch tests + prick tests + ID tests increases the yield to 72%.
- Usefulness of patch tests varies with:
  - The type of eruption
  - The causative drug.
Sensitivity of PT According to the Type of Eruption

• Most useful (Type IV)
  – Erythroderma/Eczema 76%
  – Fixed Drug Eruption 60-75%
  – Maculopapular Eruption 54%
  – AGEP 50%

• Least useful
  – Urticaria/Angioedema 11%
  – Stevens-Johnson/TEN 9%
  – Vasculitis/Pruritus 0%
Sensitivity According to Drug

- Diltiazem: 100%
- Carbamazepine: 86%
- Corticosteroids: 83%
- Amoxicillin + Clavulinic acid: 80%
- Tetrazepam: 67%
- Heparins: 36%
- Other β-lactam antibiotics: 33%
Management of drug eruption

- Withdraw medication (ideal) and replace
- Some medication require gradual taper to avoid rebound and undesirable S/E (MOA, SSRI…)
- Taper and consider po prednisone
- Topical treatment vs systemic
- Internal organ inflammation a consideration with drug eruption (CBC, LFT, RFT)
Key points

- Differentiate the cutaneous manifestation from a trigger/exacerbation from drug eruption/manifestation
- Allergic rxn based on morphology and timing principally
- Helpful test in face of certain eruptions and use dependant on type of medication, type of morphology
For hyperhidrosis

• http://www.hyperhidrosis.ca/